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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,460	10/16/2001	Daniel S. Kohane	0492611-0418 (MIT 9023)	5906

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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

9.m

Office Action Summary	Application No.	Applicant(s)	
	09/981,460	KOHANE ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-78* is/are pending in the application.

4a) Of the above claim(s) *25,28,34-36,41-44* is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24,26,27,29-33,37-40,45-70 and 72-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election without traverse of the species of DPPC as the lipid having both positive charges on the choline portion and negative charges on the phosphatidyl portion (claim 27), albumin as the protein (claim 32), lactose as the sugar (claim 38), less than 10 micrometers as the diameter of the microparticles (claim 59); and embryonic stem cells as the cells (claim 72). Note that lipids comprising phospholipid and/or a choline portion embrace the elected species, and thus, will be searched and examined therein. In addition, the species of cellulose as a sugar has been rejoined for prior art search and examination.

Claims 25, 28, 34-36, 41-44, 71, directed to non-elected species, remain withdrawn by the examiner.

Claims 1-24, 26, 27, 29-33, 37-40, 45-78, to which the following grounds remain applicable, are pending.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-24, 26, 29, 30-33, 37, 39-40, 45, 46, 47, 49-62, 65-70, 73-78 remain rejected under 35 U.S.C. 102(b) as being anticipated by Grinstaff *et al.* (US 5,639,473), or under 35 USC 103 as being unpatentable over Grinstaff *et al.* (US 5,639,473).

The main thrust of the claimed invention is the making of a matrix or microparticle composed of at least two components selected from a lipid (DPPC, any protein (albumin) and a sugar (cellulose or lactose). The microparticles can also be formulated

so as to incorporate a stabilizer such as PEG or a synthetic polymer. The size of the microparticle can be less than 50 um (less than 10 um). The microparticles are employed for delivery of any known DNA of choice such as RNA, plasmid coding a protein of interest, *e.g.,* immunogen, viral antigen, protein of choice.

Grinstaff teaches the making of a matrix or microparticle composed of at least two components selected from a lipid (lipids composed of a choline and a phospholipid), any protein (albumin) and a sugar (cellulose), *e.g.,* see column 7 bridging column 8, column 8, lines 54-65 (albumin), column 9, lines 11-20, (synthetic polymer such as PEG or polyacrylic acid), column 12, lines 12-31 (phosphatidyl choline (PC) and/or proteins and/or poysaccharides such as cellulose. Polymeric shells as carriers for polynucleotide constructs, DNA or RNA are disclosed in Example 13. The size of the microparticle can be less than 50 um (less than 10 um, see example 46). Routes of administration are disclosed on column 26, second full par. The microparticles are employed for delivery of any known DNA of choice such as RNA, plasmid coding a protein of interest, *e.g.,* immunogen, viral antigen, protein of choice. The Grinstaff reference as a whole particularly teaches that any combination of biocompatible materials such as sugar, lipid and/or protein and/or PEG can be crosslinked to make a biocompatible polymeric shell, wherein the shell or its surface can be modified to incorporate any known emulsifier, surfactant and/or stabilizer. The polymeric shell would then be suitable to encapsulate any drug of choice such as DNA, RNA or plasmid coding for a protein or antigen of interest. As such, it would also have been obvious for one of ordinary skill in the art of polymer or microparticle to employ any combination of

ratio or percent weight of each of the biocompatible material as a matter of design choice for the making of the polymeric shell, particularly since the reference clearly teaches that as long as ultrasonic radiation and crosslinkers are employed, combinations of albumin, sugar, lipids and/or PEG can be formulated to make a polymeric shell designed for use as a carrier of any biologically active molecules such as known antigen coding plasmids.

Thus, Grinstaff anticipates, or in the alternative, renders the claimed invention as a whole *prima facie* obvious.

Applicant's response has been considered (page 15 through page 16) but is not found persuasive by the examiner.

Applicant argues mainly that Grinstaff does not teach at least two components as claimed in independent claims 1-6, let alone all three components as recited in claims 1 and 2. However, the examiner maintains that he Grinstaff reference as a whole particularly teaches that any combination of biocompatible materials such as sugar, lipid and/or protein and/or PEG can be crosslinked to make a biocompatible polymeric shell, wherein the shell or its surface can be modified to incorporate any known emulsifier, surfactant and/or stabilizer. The polymeric shell would then be suitable to encapsulate any drug of choice such as DNA, RNA or plasmid coding for a protein or antigen of interest. For example, Grinstaff teaches the making of a matrix or microparticle composed of at least two components selected from a lipid (lipids composed of a choline and a phospholipid), any protein (albumin) and a sugar (cellulose), *e.g.,* see column 7 bridging column 8, column 8, lines 54-65 (albumin), column 9, lines 11-20,

(synthetic polymer such as PEG or polyacrylic acid), column 12, lines 12-31 (phosphatidyl choline (PC) and/or proteins and/or poysaccharides such as cellulose. Polymeric shells as carriers for polynucleotide constructs, DNA or RNA, including those complexed to a cationic lipid are disclosed in Example 13.

More specifically, Griinstaff teaches on column 8 about a number of suitable materials that can be used to make microparticles:

> chemical modification. For example, naturally occurring biocompatible materials such as proteins, polypeptides, oligopeptides, polynucleotides, polysaccharides (e.g., starch, cellulose, dextrans, alginates, chitosan, pectin, hyaluronic acid, and the like), lipids, and so on, are candidates for such modification. Other linkages, such as esters, amides, ethers, and the like, can also be formed during the ultrasonic irradiation step (so long as the requisite functional groups are present on the starting material).
>
> As examples of suitable biocompatible materials, naturally occurring or synthetic proteins may be employed, so long as such proteins have sufficient sulfhydryl or disulfide groups so that crosslinking (through disulfide bond formation, for example, as a result of oxidation during ultrasonic irradiation) can occur. Examples of suitable proteins include albumin (which contains 35 cysteine residues), insulin (which contains 6 cysteines), hemoglobin (which contains 6 cysteine residues per $\alpha_2\beta_2$ unit), lysozyme (which contains 8 cysteine residues), immunoglobulins, α-2-macroglobulin, fibronectin, vitronectin, fibrinogen, and the like, as well as combinations of any two or more thereof.

In addition to a teaching by Grinstaff as indicated above regarding an addition or incorporation of at least one, two or a combination of suitable agent such as lipids and/or sugar to enhance the structural integrity of the polymeric shell composed of a chosen biocompatible material such as an albumin, Grinstaff teaches the same on column 12:

> In addition, the polymeric shell can optionally be modified by a suitable agent, wherein the agent is associated with the polymeric shell through an optional covalent bond. Covalent bonds contemplated for such linkages include ester, ether, urethane, diester, amide, secondary or tertiary amine, phosphate ester, sulfate ester, and the like bonds. Suitable agents contemplated for this optional modification of the polymeric shell include synthetic polymers (polyalkylene glycols (e.g., linear or branched chain polyethylene glycol), polyvinyl alcohol, polyhydroxyethyl methacrylate, polyacrylic acid, polyethyloxazoline, polyacrylamide, polyvinyl pyrrolidinone, and the like), phospholipids (such as phosphatidyl choline (PC), phosphatidyl ethanolamine (PE), phosphatidyl inositol (PI), sphingomyelin, and the like), proteins (such as enzymes, antibodies, and the like), polysaccharides (such as starch, cellulose, dextrans, alginates, chitosan, pectin, hyaluronic acid, and the like), chemical modifying agents (such as pyridoxal 5'-phosphate, derivatives of pyridoxal, dialdehydes, diaspirin esters, and the like), or combinations of any two or more thereof.

A further addition of PEG to the shell polymer so as to enhance the bioavailability of the matrix is also taught explicitly by Grinstaff on column 12:

> Variations in the polymeric shell are also possible. For example, a small amount of PEG containing sulfhydryl groups could be included with the polymer. Upon exposure to ultrasonic irradiation, the PEG is crosslinked into the polymer and forms a component of the polymeric shell. Alternatively, PEG can be linked to the polymeric shell following the preparation of the shell (rather than being included as part of the media from which the shell is prepared).

Applicant further argues while the materials used in Grinstaff must undergo cross-linking during ultrasonic irradiation to be useful, applicant's claimed invention does not claim such. However, the claims are read as reasonably broad as possible,

and thus, to the extent that applicant 's claims simply recite microparticles comprising a polynucleotide encapsulated in a matrix comprising at least three components selected from a ipid, protein, and sugar or a lipid, and synthetic polymer, applicant 's claims do embrace the microparticles as set forth in Grinstaff, regardless of whether or not applicant intend to employ a sulfhydryl group for cross-linking. Should applicant intend to claim a particular structure that could distinguish from that of Grinstaff, the claims should be amended to reflect such intention. Otherwise, the claims remain properly anticipated by the microparticles of Grinstaff.

Claims 1-24, 26, 27, 29-33, 37-40, 45-69, 73-78 was rejected under 35 USC 102(e) or 102(a) as being anticipated by Edwards (US 5,985,309), or in the alternative, under 35 USC 103(a) as being unpatentable over Edwards (US 5,985,309).

Applicant in the response filed March 18, 2004 filed the Langer Declaration, which states that the invention that anticipates the claims of this application was not invented by another. This rejection has been withdrawn by the examiner as the result of the Declaration, and as a result of the claims in the '309 being directed to not the same patentable invention as that in this instant application.

Claims 1-24, 26, 27, 29-33, 37-40, 45-78 remain rejected under 35 USC 103 as being unpatentable over Grinstaff taken with Wheeler (US 5,976,567).

The rejection of the base claims is applied here as indicated above in the 102 rejections.

To the extent that Grinstaff does not teach that the lipid surfactant can be DPPC, and that the carriers or particles can be used to transducer hematopoietic stem cells or embryonic stem cells *in vitro* and/or *in vivo,* Wheeler teaches that DPPC-based carriers (column 8, line 60) can be used to enhance the transfection and delivery of lipid/nucleic acids complexes into hematopoietic stem cells or embryonic stem cells *in vitro* and/or *in vivo* (column 28, lines 34-47).

It would have been obvious for one of ordinary skill in the art to employ any choline-based phospholipids such as DPPC in the lipid coated polymeric shell of Grinstaff. One of ordinary skill in the art would have been motivated to do so because Grinstaff teaches that any choline based phospholipids can be incorporated in the polymeric shell based carrier and that DPPC, as evidenced by Wheeler, is commonly used in the prior art as non-cationic lipids so as to adjust the hydrophobic properties and/or lipid bilayer forming properties in the making of a DNA delivery based lipid carrier.

It would also have been obvious for one of ordinary skill in the art to employ the polymeric shell of Grinstaff to delivery and/or transducer embryonic stem cells *in vitro* or *in vivo.* One of ordinary skill in the art would have been motivated to do so because it is well-established in the prior art, as exemplified by Wheeler, that lipid nucleic acid particles can be used to enhance the DNA delivery and transfection into embryonic stem cells *in vitro* and/or *in vivo.*

Thus, the claimed invention, as a whole, was *prima facie* obvious.

Applicants' comments (page 16 bridging page 17) also have been considered by

the examiner but is not found persuasive for the same reasons as set forth in the stated rejections and the reasoning as addressed in the preceding paragraphs.

Furthermore, in order to support the examiner's rebut to applicant's response, the following references are further cited to indicate that it is well-established in the prior art of record that microparticles composed of at least three components selected from a sugar, protein, lipid and polymer are routinely made by a skilled artisan, and the Grinstaff reference is just one of many exemplified references that is currently applied in the ground of the rejection as set forth in the main body of the office action.

1/ Hanes (US 5,855,913) teaches a polymeric microparticle of less than 10 um in diameter for use as a controlled release- encapsulated carrier of biologically active molecules such as DNA or DNA coding for a gene of interest, wherein the microparticles are composed of a combination of biocompatible materials selected from DPPC, copolymers, protein exipients (any known polymeric polyeptide or copolymers thereof) and a sugar (lactose), *e.g.,* entire disclosure including claims, column 3 bridging column 4, column 4 bridging column 5, entire column 6, column 6 bridging column 7, column 7, lines 4-68, column 8, lines 7-19, column 11 through column 12.

2/ Edwards (US 2004/0076589 A1) teaches on par. 0064 that microparticles composed of PLGA/DPPC/charged functional groups such as an amino acid can be made for delivery of a biologically active agent by aerosol. Batycky (US 6,586,008) teaches the same on columns 7 and 8.

3/ Sankaram (US 6,277,413) teaches polymeric matrix carrier composed of

biodegradable polymers such as polypeptides and a synthetic polymer and lipids (columns 7 and 8).

4/ Unger (US 2001/0031740) teaches on claims 1,2 and 39 that lipid carriers bearing a sulfonated saccharide can be used as a delivery vehicle.

5/ Bellhouse (US 6,685,669) teaches on column 4 that a delivery composition comprising a carrier such as gelatin, excipients such as lactose, and a charged lipid is routinely made to deliver a therapeutic agent.

6/ Sutton (US Pat No. 6,204,054) teaches on the last par. of column 7 that hydrophilic stabilizers such as a sugar and/or polymer can be incorporated to a delivery vehicle comprising a functionally active albumin.

7/ Mori (US Pat No. 5,776,488) teaches on column 1 that it is well known in the prior art that lipsomal carriers comprising a fatty acid, PEG and a sugar have been made to encapsulate an anti-tumor agent.

8/ Rypacek (GB 2 174 097 A) teaches that a polymeric stabilizer such as a poly(alpha-amino acid) can be used in the making of spherical microparticles of starch dextran or human serum albumin (entire disclosure).

The following is a new ground of rejection:

The Declaration while obviates the 102(e) or 102(a) rejection is not found persuasive to remove a new ground of rejection as set forth below. The newly applicable prior art is the parent application of the '309 patent, having a serial No. 08/784,421, issued as US pat No. 5,855,913, which also has a 102(b) date (1/5/99) against the effective filing dated of this instant application (10/16/2000).

In view of the immediately preceding paragraphs,

Claims 1-24, 26, 27, 29-31, 33, 37-40, 45-69, 73-78 are rejected under 35 USC 102(b) as being anticipated by Hanes (US 5,855,913), or in the alternative, under 35 USC 103(a) as being unpatentable over Hanes (US 5,855,913).

Hanes teaches a polymeric microparticle of less than 10 um in diameter for use as a controlled release- encapsulated carrier of biologically active molecules such as DNA or DNA coding for a gene of interest, wherein the microparticles are composed of a combination of biocompatible materials selected from DPPC, copolymers, protein excipients (any known polymeric polyeptide or copolymers thereof) and a sugar (lactose), *e.g.,* entire disclosure including claims, column 3 bridging column 4, column 4 bridging column 5, entire column 6, column 6 bridging column 7, column 7, lines 4-68, column 8, lines 7-19, column 11 through column 12.

In other words, Hanes teaches that any combination of biocompatible materials such as therapeutic agents, polymers, lipid surfactants and protein/sugar excipients can be used to make the encapsulated particles so that the particles are basically formulated to become polymeric microparticles for drug delivery to the pulmonary system, wherein the particles having an appropriate size such as at least 5 microns in diameter, and wherein the polymeric particles are capable of biodegrading at a controlled rate for delivery of a drug (see column 5, last full par.), and column 7 through column 8. Example 3 discloses a combination of a lipid, a sugar, and a polymer for the making of exemplified microparticles.

Hanes also teaches on column 6 (last par.) that the polymeric particles are

preferably prepared by spray drying, and that the size of the particles can be between 5 and 30 um in diameter. Polymer and/or co-polymers concentrations can be used, for example, between 0.05 and 1.0 g/ml. Furthermore, Hanes teaches (columns 7-8) that depending on a preference of particularly desired aerodynamic properties of inhaled microparticles, the spray drying parametes such as concentrations of the surfactants, polymers and exipients can be adjusted accordingly by a person of ordinary skill in the art.

To the extent that Hanes do not teach explicitly minor modifications such as known DNAs, RNA or plasmids encoding for an antigen, ratios of agents being used in the formulations, and/or a particular combination of known matrix polymers, lipids and excipient(s), such would have been obvious to one of ordinary skill in the art as minor modifications that can be practiced as a mater of design choice by a person of an ordinary skill in the art of polymer.

Thus, Hanes anticipates, or in the alternative, renders the claimed invention as a whole *prima facie* obvious.

Claims 1-24, 26, 27, 29-33, 37-40, 45-69, 73-78 are rejected under 35 USC 103 as being unpatentable over Hanes taken with any of Grinstaff, Sutton, or Rypacek, and further in view of Wheeler.

The rejection of the base claims are applied here as indicated above.

While Hanes do no claim explicitly minor modifications such as known DNAs, RNA or plasmids encoding for an antigen, ratios of agents being used in the

formulations, and/or a particular combination of known matrix polymers (albumin and/or other known polymer), lipids and excipient(s) such as any other sugar (cellulose), such would have been obvious to one of ordinary skill in the art as minor modifications that can be practiced as a mater of design choice by a person of an ordinary skill in the art of polymer, particularly in view of the totality of the prior art of record as set forth in Grinstaff, Sutton, or Rypacek, wherein each of which clearly teaches that a combination of a polymeric polypeptide such as albumin can be used in a combination of other polymer and/or suitable excipients such as lipid and/or sugar in order to make a suitable delivery microparticle composition for a delivery of choice.

Thus, it would have been obvious for one of ordinary skill in the prior art to employ albumin as an at least one of the suitable polymers in the making of polymeric microparticles of Hanes. One would have been motivated to do so because the totality of the prior art of record teaches that albumin can be used as a biodegradable material in the making of a polymeric microparticle.

It would also have been obvious for one of ordinary skill in the art to employ the polymeric shell of Grinstaff to delivery and/or transducer embryonic stem cells *in vitro* or *in vivo*. One of ordinary skill in the art would have been motivated to do so because it is well-established in the prior art, as exemplified by Wheeler, that lipid nucleic acid particles can be used to enhance the DNA delivery and transfection into embryonic stem cells *in vitro* and/or *in vivo*. See column 8, line 60, column 28, lines 34-47).

Thus, the claimed invention, was *prima facie* obvious.

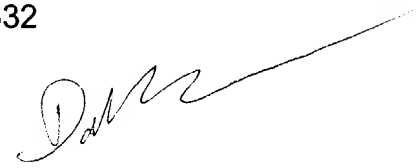
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(571-272-0731)**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson* may be reached at **571-272-0804.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Trong Nguyen
Primary Examiner
Art Unit: 1632



DAVE T. NGUYEN
PRIMARY EXAMINER